



in which:

X_1, X_2, X_3, X_4 , which may be the same or different from one another, is selected from the group consisting of $-\text{CONR}-$, $-\text{NRCO}-$, $-\text{OCO}-$, $-\text{COO}-$, $-\text{CH}_2\text{NR}-$ and $-\text{NR-CH}_2-$, where R is H or a C_{1-3} alkyl or benzyl;

f, g, h, m, which may be the same or different from one another, represent a number selected from the group consisting of 0, 1 and 2;

R_1 and R_2 , which may be the same or different from one another, represent a $-(\text{CH}_2)_r-$ Ar group, where $r = 0, 1, 2$ and where Ar is an aromatic group selected from the group consisting of: benzene, naphthalene, thiophene, benzothiophene, pyridine, quinoline, indole, furan, benzofuran, thiazole, benzothiazole, imidazole, and benzo-imidazole, said Ar group being possibly substituted with a maximum of two residues selected from the group consisting of C_{1-3} alkyl or halo-alkyl, C_{1-3} alkoxy, C_{2-4} amino-alkoxy, halogen, OH, NH_2 , and $\text{NR}_{13}\text{R}_{14}$ where R_{13} and R_{14} , which may be the same or different from one another, represent hydrogen or C_{1-3} alkyl; wherein R_3 is selected from the group consisting of:

-hydrogen,

-linear or branched alkyl having the formula $\text{C}_n\text{H}_{2n+1}$, with $n = 1-5$, cyclo-alkyl or alkylcyclo-alkyl groups having the formula $\text{C}_n\text{H}_{2n+1}$, with $n = 5-9$,

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-(CH₂)_r-Ar₁ group, where r= 0, 1, 2 and where Ar₁ is an aromatic group selected from the group consisting of: benzene, naphthalene, thiophene, benzothiophene, pyridine, quinoline, indole, furan, benzofuran, thiazole, benzothiazole, imidazole, and benzoimidazole, said Ar₁ group being possibly substituted with a maximum of two residues selected from the group consisting of C₁₋₃ alkyl or halo-alkyl, C₁₋₃ alkoxyl or aminoalkoxyl, halogen, OH, NH₂ and NR₁₃R₁₄ where R₁₃ and R₁₄, which may be the same or different from one another, represent hydrogen or C₁₋₃ alkyl;

wherein R₄ is selected from the group consisting of:

-hydrogen or C₁₋₆ alkyl,

-L-Q, where L is a chemical bond or a linear or branched C₁₋₆ alkyl residue and Q is selected from the group consisting of:

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i) H, OH, OR₉, NH₂, NR₉R₁₀, guanidine, sulfate, phosphonate and phosphate where R₉ and R₁₀, which may be the same or different from one another, represent a hydrogen C₁₋₃ alkyl group, C₁₋₃ hydroxyalkyl, C₁₋₃ dihydroxyalkyl, C₁₋₃alkyl-CONHR₁₂, C₁₋₃alkyltetrazole, C₁₋₃alkyl-COOH or wherein R₉R₁₀ joined together form with the N-atom a saturated 4-6 membered heterocycle possibly containing a further heteroatom selected from the group consisting of N, O and S and wherein R₁₂ is a mono-, di-, tri-glycosidic group possibly protected with one or more C₁₋₃-acyl groups or substituted with amino-groups or C₁₋₃ acylamino-groups;

ii) COOH, tetrazole, SO₂NH₂, SO₂NHCOOR₈, CONHR₈, NHCOR₈, where R₈ represents a linear or cyclic C₁₋₆ alkyl chain containing one or more polar groups selected from the group consisting of: OH, NR₁₅R₁₆, COOH, CONHR₁₂, PO₃H and SO₃H, OR₁₁ and where R₁₅ and R₁₆, which may be the same or different from one another, represent a hydrogen or C₁₋₃ alkyl group, and where R₁₁ is a C₁₋₃ alkyl or C₂₋₄ amino-alkyl chain, R₁₂ is a mono-, di-, tri-glycosidic group possibly protected with one or more C₁₋₃acyl groups or substituted with amino-groups or C₁₋₃acylamino-groups or R₁₅R₁₆ joined together form with the N-atom a saturated 4-6 membered heterocycle possibly substituted with C₁₋₃alkyl-groups or with saturated 4-6 membered heterocycle-groups containing at least an N-atom;

iii) COOR₁₇, CONHR₁₂, OR₁₂ where R₁₂ is a mono-, di-, tri-glycoside group

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possibly protected with one or more C_{1-3} acyl groups or substituted with amine or C_{1-3} acylamine groups and R_{17} is a group R_{12} as above defined or a group C_{1-3} alkyl, C_{1-3} alkylphenyl, wherein the phenyl-group can be substituted with a group OH, NO_2 , NH_2 , CN , CH_3 , Cl, Br;
 R_5 , R_6 , R_7 , which may be the same or different from one another, represent a hydrogen or C_{1-3} alkyl group; with the proviso that when R_1 or R_2 are benzyl or 4-hydroxybenzyl then R_3 and R_4 are isopropyl and an acceptable salt or enantiomer thereof.

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2. (Amended) Compound according to Claim 1, in which:

f, g, h, m, which may be the same or different from one another, may be 0 or 1;

R_1 and R_2 which may be the same or different from one another, represent the side chain of a natural amino acid selected from the group consisting of tryptophan, phenylalanine, tyrosine and histidine, or the side chain of a non-natural amino acid selected from the group consisting of:

tryptophan and phenyl alanine, either mono- or di-substituted with residues selected from the group consisting of C_{1-3} alkyl or halo-alkyl, C_{1-3} alkoxy or amino-alkoxy, halogen, OH, NH_2 and $NR_{13}R_{14}$, where R_{13} and R_{14} , which may be the same or different from one another, represent a hydrogen or C_{1-3} alkyl group;

R_3 is selected from the group consisting of:

– linear or branched alkyl having the formula C_nH_{2n+1} with $n = 1-5$ (selected from the group consisting of methyl, ethyl, propyl, isopropyl, n-butyl and t-butyl) cycloalkyl or alkylcycloalkyl of formula C_nH_{2n-1} with $n = 5-9$ (selected from the group consisting of cyclopentyl, cyclohexyl and methylcyclohexyl)

$-(CH_2)_r-Ar_1$, where $r = 1$ or 2 and where Ar_1 is an aromatic group selected from the group consisting of: α -naphthyl, β -naphthyl, phenyl, indole, said Ar_1 group being possibly substituted with a maximum of two residues selected from the group consisting of: C_{1-3} alkyl, CF_3 , C_{1-3} alkoxy, Cl, F, OH and NH_2 ;

R_4 represents an L-Q group where:

L is a chemical bond or CH_2 , and

Q is selected from the group consisting of:

– OH, NH₂, NR₉R₁₀, OR₁₁, and where R₉ and R₁₀, which may be the same or different from one another, represent a hydrogen or C₁₋₃ alkyl group, C₁₋₃hydroxy alkyl, C₁₋₃dihydroxyalkyl, C₁₋₃alkyl-CONHR₁₂ (wherein R₁₂ is a monoglycosidic group derived from D or L pentoses or hexoses (selected from the group consisting of ribose, arabinose, glucose, galactose, fructose, glucosamine and galactosamine and their N-acetylated derivatives)), C₁₋₃alkyltetrazole, C₁₋₃alkyl-COOH or wherein R₉R₁₀ are joined together to form with the N atom a morpholine or a piperidine ring and where R₁₁ is a C₁₋₃ alkyl chain, or a C₂₋₄ amino-alkyl chain; NHCOR₈ wherein R₈ is a cyclohexane containing from 2 to 4 OH groups, C₁₋₆ alkyl chain containing a polar group (chosen in the group consisting of NH₂, COOH, CONHR₁₂, (wherein R₁₂ is as hereabove defined) or [1,4']bipiperidine) – COOH, COOR₁₇ or CONHR₁₂, wherein R₁₂ is as hereabove defined and R₁₇ is as R₁₂ or a group 4-nitrobenzyl.
– R₅, R₆, R₇ are H,
in which the carbon atom that carries the substituents R₃ and R₇ has configuration R.

3. (amended twice) A compound according to Claim 2 selected from:

- (a) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH₂C₆H₅)-CH₂-NH]}
- (b) Cyclo{-Suc-Trp-Phe-[(S)-NH-CH(CH₂C₆H₅)-CH₂-NH]}
- (c) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH₂C₆H₁₁)-CH₂-NH]}
- (d) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH₂C₆H₄(4-OCH₃))-CH₂-NH]}
- (e) Cyclo{-Suc-Trp(5F)-Phe-[(R)-NH-CH(CH₂C₆H₅)-CH₂-NH]}
- (f) Cyclo{-Suc-Trp(Me)-Phe-[(R)-NH-CH(CH₂C₆H₅)-CH₂-NH]}
- (g) Cyclo{-Suc-Phe(3,4-Cl)-Phe-[(R)-NH-CH(CH₂C₆H₅)-CH₂-NH]}
- (h) Cyclo{-Suc-Trp-Phe(3,4-Cl)-[(R)-NH-CH(CH₂C₆H₅)-CH₂-NH]}
- (i) Cyclo{-Suc-Trp-Tyr-[(R)-NH-CH(CH₂C₆H₅)-CH₂-NH]}
- (j) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH₂C₆H₃-3,4-diCl)-CH₂-NH]}
- (k) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH₂C₆H₄-4-OH)-CH₂-NH]}
- (l) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH₂-CH₂-C₆H₅)-CH₂-NH]}

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cont.
- (m) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH₂-2-naphthyl)-CH₂-NH]}
- (n) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH₂-indol-3-yl)-CH₂-NH]}
- (o) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH₂-5-F-indol-3-yl)-CH₂-NH]}
- (p) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₄-3-F)-CH₂-NH]}
- (q) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₃-3,4-diF-CH₂-NH)-]}
- (r) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₄-4-CF₃-CH₂-NH)-]}
- (s) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH₂-CH(CH₂C₆H₅)-NH]}
- (t) Cyclo{-Suc-Trp-Phe-[(S)-NH-CH₂-CH(CH₂C₆H₅)-NH]}
- (u) Cyclo{-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]-(CH₂)₃CO-}
- (v) Cyclo{-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-N(CH₃)-(CH₂)₃CO-}
- (w) Cyclo{-Suc[1(S)-NH₂]-Trp-Phe-[(R)NH-CH(CH₂-C₆H₅)-CH₂NH]-}
- (x) Cyclo{-Suc[1(R)-NH₂]-Trp-Phe-[(R)NH-CH(CH₂-C₆H₅)-CH₂NH]-}
- (y) Cyclo{-Suc[2(S)-NH₂]-Trp-Phe-[(R)NH-CH(CH₂-C₆H₅)-CH₂NH]-}
- (z) Cyclo{-Suc[2(R)-NH₂]-Trp-Phe-[(R)NH-CH(CH₂-C₆H₅)-CH₂NH]-}
- (aa) Cyclo{-Suc[1(S)-NH(CH₃)]-Trp-Phe-[(R)NH-CH(CH₂-C₆H₅)-CH₂NH]-}
- (ab) Cyclo{-Suc[1-COO(CH₂-C₆H₄-4-NO₂)]-Trp-Phe-[(R)NH-CH(CH₂-C₆H₅)-CH₂NH]-}
- (ac) Cyclo{-Suc(1-COOH)-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]}
[Cyclo{-Suc(1-COOH)-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]}]
- (ad) Cyclo{-Suc(1-OH)-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]}
- (ae) Cyclo{-Suc(2-COOH)-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]}
- (af) Cyclo{-Suc(2-OH)-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]}
- (ag) Cyclo{-Suc[1(S)-(2H-tetrazolyl-5-ylmethyl)amino]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]-} trifluoro-acetic acid
- (ah) Cyclo{-Suc[1(S)-(morpholin-4-yl)]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]-} trifluoroacetic acid
- (ai) Cyclo{-Suc[1(S)-N(CH₃)₂]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]-} trifluoroacetic acid
- (aj) Cyclo{-Suc[1(S)-(piperidin-4-yl)]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]-} trifluoroacetic acid
- (ak) Cyclo{-Suc[1(S)-(N(CH₂CH₂OH)₂)]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]-} trifluoroacetic acid

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- (al) Cyclo{-Suc[1(S)-(N(CH₂CH(OH)CH₂OH)]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]-} trifluoroacetic acid
- (am) Cyclo{-Suc[1(S)-(3-carboxypropanoyl)amino]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]-}.
- (an) Cyclo{-Suc[1(S)-[3-N'-β-D-glucopiranos-1-yl]-carboxamidopropanoyl]amino]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]-}
- (ao) Cyclo{-Suc[1(S)-[(carboxymethyl)amino]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]-} trifluoroacetic acid
- (ap) Cyclo{-Suc[1(S)-[N'-β-D-glucopiranos-1-yl]-carboxyamideomethyl]amino]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]-} trifluoroacetic acid
- (aq) Cyclo{-Suc[1(S)-(chiny)amine]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]-}
- (ar) Cyclo{-Suc[1(S)-(4-aminobutanoyl)amino]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]-} trifluoroacetic acid
- (as) Cyclo{-Suc[1(S)-[1,4']bipiperidin-1-yl]acetamido]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]-} trifluoroacetic acid
- (at) Cyclo{-Suc[1(S)-[N-(β-D-glucopiranos-1-yl)-carboxyamido]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]-}
- (au) Cyclo{-Suc[1(S)-[N'-(2-N-acetyl-β-D-glucopiranos-1-yl)-carboxyamido]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]-}.

B7 Sub C3

5. (Amended) A composition comprising a compound of general formula (I) according to Claim 1 in combination with a suitable carrier or excipient..

6. (Amended) A composition according to Claim 5, adapted for use as a tachykinin antagonist.

7. (Amended) A composition according to Claim 6, adapted for use as an antagonist of the human neurokinin-2 (herein NK-2) receptor.

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8. (Amended) A composition according to Claim 7, adapted for use in the treatment of the bronchospastic and inflammatory component of asthma, coughing, pulmonary

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irritation, intestinal spasms, spasms of the biliary tract, local spasms of the bladder and of the ureter during cystitis, and kidney infections and colics.

B8 Sub C5
12. (Amended) A method of antagonizing an NK-2 receptor in a mammal afflicted with asthma comprising contacting an NK-2 receptor in said mammal with a compound according to Claim 1 for a time and under conditions effective to antagonize an NK-2.

13. (Amended) A method of antagonizing an NK-2 receptor in a mammal afflicted with an anxiety disorder comprising contacting an NK-2 receptor with a compound according to Claim 1 for a time and under conditions effective to antagonize an NK-2 receptor.

B9 Sub C6
14. (Amended) A method for the treatment of the bronchospastic and inflammatory component of asthma, coughing, pulmonary irritation, intestinal spasms, spasms of the biliary tract, local spasms of the bladder and if the ureter during cystitis, and kidney infections and colics, in which quantities of between 0.02 and 10 mg/kg of body weight of active principle consisting [of products] of formula (I), according to Claim 1, are administered to the patient for a time and under conditions effective to antagonize an NK-2 receptor.

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16. (New) A method of antagonizing a neurokinin-2 (NK-2) receptor comprising contacting an NK-2 receptor with a compound according to claim 1 for a time and under conditions effective to antagonize said NK-2 receptor.

17. (New) A method of antagonizing a neurokinin-2 (NK-2) receptor comprising administering to a mammal in need thereof a compound according to claim 1 for a time and under conditions effective to antagonize the NK-2 receptor.

18. (New) The method according to claim 17 wherein said mammal is afflicted with a disorder selected from the group consisting of the bronchospastic and inflammatory component of asthma, coughing, pulmonary irritation, intestinal spasms, spasms of the biliary tract, local spasms of the bladder and of the ureter during cystitis, and kidney infections and colics.